

I

TREATMENT OF WASSERMANN-FAST SYPHILIS *

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MR. PRESIDENT,—First of all I must express to you, and to the Council of the Society, my high appreciation of the honour you have done me by inviting me to read this paper.

Coming, as I do, from the remote province of Salford, which, city though it be, is regarded by most people as a mere adjunct to, and by some as an excrescence upon, its mighty neighbour Manchester; coming, as I say, from the exterior darkness into the full blaze of the metropolis, I feel a certain degree of misgiving lest that which I am able to contribute may not be quite adequate to the occasion.

I feel encouraged, however, when I think of the kindly reception invariably accorded to the stranger within the gates. And if, in the course of to-night's proceedings, there emerge points upon which we are not all in complete agreement, I would gently direct your attention to that fact which has such a profound influence upon our national life—the fact that “what Manchester (and Salford) think to-day, the rest of England thinks to-morrow!”

My great regret this evening is that I cannot appear in the *rôle* of one of the wise men from the East; and so it is that I do not carry in my hands the triple gifts—the gold of a painstaking laboratory research, the frankincense of some new therapeutic discovery, or myrrh culled from the researches of others.

On the contrary, I come practically empty-handed; or at most, bearing but my own miserable rush-light of personal experience. But, such as it is, I have the hope that it may serve to kindle a good fire of discussion, and that at the end of it each one may depart unto his own place carrying something away, even if it be only a resolu-

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tion to avoid some of the mistakes which we are convinced are committed by our colleagues.

Differences of opinion there must be, and it is only by amicable discussion of them that progress can be made.

There will, I imagine however, be general agreement with the statement that one of the hardest problems presenting itself to the syphilologist for solution is that involving the correct ætiology, interpretation and proper handling of syphilitics whose sera, in spite of active and prolonged treatment, yield persistently positive results.

As a preliminary to a discussion of these matters, it is necessary to postulate certain things and to define certain terms.

First of all it must be taken for granted that the diagnosis of syphilis is correct; and secondly, that the patient has received treatment of sufficient quantity, quality and duration as experience has shown to have the usual effect of rendering the serology permanently negative.

What criteria are we to adopt for each of these two things? We must, I think, for the present, take a positive Wassermann as the criterion of diagnosis; and, furthermore, that a persistently positive result in a treated patient indicates *uncured syphilis*. And we can, I think, even go a little farther than that, and reason that a persistently positive serology points to the fact that the treatment given to that particular patient—however well it may work in the majority of cases—has in this instance been inadequate in some one or more respects.

Warthin states that he has never seen in the post-mortem room a case of cured syphilis. When he made that statement at the British Medical Association meeting in Manchester last year, it aroused in many of his auditors a feeling of alarm and despondency. Those were they who jumped to the conclusion that Warthin's findings meant that syphilis is incurable, and that all that modern therapy can do is to beat the disease into a more or less avirulent state. That, indeed, would seem to be Warthin's own opinion.

With such a view, I, for one, am in complete disagreement. I can discover no indication for pessimism in this matter, even though I realise that some of these post-mortem uncured cases may have, during life, exhibited a negative serology.

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What Warthin's experience does most certainly indicate is that the treatment meted out to these cases was insufficient in some respect. It failed to destroy all the infecting organisms. The remedial agents may have been wrongly chosen, wrongly manipulated, the duration of treatment may have been too short, or some such thing—but in the last analysis the fact remains that, whatever may have been the cause, these patients were uncured of their syphilis.

Although serologically negative, these cases are really identical with those which are Wassermann-fast—they mean *uncured syphilis*. The only difference is a superficial apparent one, and lies in this: that the uncuredness of Wassermann-fast cases is discoverable during life.

The point I am trying to make here is that while a persistently positive serology in a treated case undoubtedly indicates uncured syphilis, a negative serology in such cases does not necessarily imply that the disease has been eradicated. The securing of a permanently negative Wassermann is eminently desirable; it is an attainable objective, but it is not the "journey's end." It is, however, an important milestone on the road.

Warthin's work would seem to show that the attainment of this milestone seldom means that the patient is cured. We must look well beyond the permanent negative and find an answer to the question of how far beyond that must treatment be pushed in order to sterilise the patient. It seems clear that the answer to this must be provided by the histologist, and not by the serologist.

The one very important lesson to be derived from Warthin's researches—and it is one which has a very intimate and practical bearing upon our subject to-night—is this: that until such time as these and similar post-mortem findings upon treated syphilitics are carefully "checked up" against the treatment given during life, we shall continue working in the dark as to the proper management of our cases. Until some such thing is done we may be actually manufacturing sero-negative cases of uncured syphilis.

Such a task is a fairly big proposition, but I think that in the immediate future, when those large hospitals, especially the poor-law hospitals, in which many of our past, present and to-come syphilitic patients will die from things other than syphilis—when these hospitals

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come under the control of the local authorities who also administer the venereal diseases scheme, then there will occur an admirable opportunity for carrying out this work.

All patients upon whom an autopsy is permitted should have those organs and tissues for which the *Treponema pallidum* has a predilection examined for syphilis by a histologist—and the previous history of such patients should be dug up so far as syphilis and anti-syphilitic treatment is concerned. I can see no other way in which to reach the information that we undoubtedly require.

The syphilologist must keep track of his patient and follow him, long after his cure, even into the post-mortem room ; for there alone can he see how many of his alleged cures are real, and what lines of treatment are most successful.

I mention this aspect of the question in passing, because I think it is sometimes forgotten that when we have solved the problem of Wassermann fastness, that of the cure of syphilis still remains. The answer to that can only be decided by a histological examination of the tissues of the dead treated syphilitic. A positive serology is only a symptom of syphilis ; and indeed there would appear to be much to support the contention that the majority of existing syphilitics are serologically negative—at least, when the full provocative procedure is not adopted.

I believe that, with proper handling, cases of early syphilis at least can not only be clinically and serologically, but also histologically, cured : in other words, that the human body can be completely sterilised so far as the *Treponema pallidum* is concerned. That is the ultimate objective of our therapy.

But for practical purposes, at the present moment we are compelled to rely upon the Wassermann test. The very least we must aim at is to render our cases permanently negative. And here I use the term “ Wassermann ” in a generic more than in a specific sense. I mean that we are compelled to shape our therapeutic course in accordance with the serological compass and keep the bow of the ship directed towards the negative pole.

A positive serology, then, must be taken to mean the presence of living treponemata actually causing, or

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capable of causing, damage. The end of treatment is the destruction of these organisms.

Unless we accept the postulate that a positive Wassermann means syphilis requiring treatment, then the discussion cannot even begin. The view is held by some, I know, that a persistent positive serology is not an indication for further therapy, but I am quite unable to follow the reasoning upon which such an opinion is based. It appears to be in accord neither with clinical nor with pathological experience.

There appear to be two classes of case which come within our purview :

Firstly, there is the syphilitic whose serological reaction immediately after treatment is negative, but, after a variable interval, again becomes positive, perhaps in an increasing degree as the time-period from the cessation of treatment lengthens.

Secondly, there is the syphilitic whose serum at no period ever recedes into a negative.

What interpretation is to be put upon each case? Do they each mean the same thing? Is the first case which shows a negative and then relapses into a positive to be considered Wassermann-fast? Or does it merely indicate that treatment has been inefficient? I believe the latter to be the correct explanation, and that such cases, while not actually Wassermann-fast, can be, and very often are, easily converted to that condition.

Now, in order to differentiate between these two types of cases—Wassermann-relapse and Wassermann-fastness—and to arrive at a real conception of what the latter is, how it arises, how it may be avoided, and in what manner it may be overcome, there falls to be considered what, I am sure, is the crux of the whole problem, namely, what is adequate treatment?

Quot homines, tot sententiæ! There are many different schools of treatment, and each can put up some sort of defence for the faith that is in it. There are widely divergent views—some diametrically opposed to others. There are differences of opinion, not only as to the drugs used, but as to the dosage, the routes of administration, and whether they should be given concurrently or in alternating series. Some hold that treatment should be continuous, others that it should be interrupted by rest-periods. It is all very difficult and somewhat chaotic,

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but the various opinions may be grouped into two schools :

- (1) That which, using arsenobenzene compounds and bismuth (or mercury), administers these concurrently ; and
- (2) That which, using the same remedial agents, administers them in alternating series.

Some of you are probably aware that my tent is pitched in the latter camp, and it was not set up in that place without having sampled the other site. And I am, of course, aware that in this room to-night, because of my adherence to the alternating principle, I am—if not in a state of splendid isolation—at least in a distinct minority. Nevertheless, since my view of Wassermann-fastness is necessarily coloured by and based upon my schemes of treatment, I propose to explain briefly what these principles are, for, as the Arab proverb elegantly puts it, “Every man thinks his own fleas the best !”

In considering this question of Wassermann-fastness, I have endeavoured to focus the matter clearly in my mind by conceiving syphilis as divisible into two main stages :

- (1) Early syphilis, and
- (2) Late syphilis.

I have brought with me some copies of the schemes of treatment which are in operation in my clinic, and upon which I have been working for nearly ten years.* Early syphilis is represented by the top row—numbers 1 to 4. Late syphilis is represented by the lower row. Of course, these standards are, to a certain degree, arbitrary, but they serve as a fixed point from which to work.

By *early* syphilis, then, I mean those cases of the disease belonging to the primary and secondary phases, in which we know from experience that whatever visceral involvement there may be, presents as a rule no clinical signs, and that the structural damage is trifling, temporary, and reparable.

By *late* syphilis—and here you will observe that I include the congenital variety—I mean that condition in which visceral structural damage is the predominating feature in the picture. It is severe, permanent, and to a greater or lesser degree irreparable. The tendency is one of progress towards fibrosis.

Let us take early syphilis first. The diagnosis is

* These are shown as an Appendix at the end of this paper.

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established either by the demonstration of the *Treponema pallidum* or by the positive serology.

Owing to changes of clinics, I have not now complete access to all the records, but, including private patients, I have investigated the records of 211 cases of early syphilis during the period from 1920 to 1927. From 1928 to the end of 1929 I have the records of 301 patients also suffering from early syphilis, who likewise have been treated according to the alternating method. Upon that material, my ten years' experience is this: that by the adoption of schemes 1 to 4 in cases which had received no previous treatment, and in which the schemes were carried through according to schedule, I have yet to encounter the first one which has failed to exhibit a negative result at the end of the course, or which has ever shown a positive thereafter in spite of repeated provocation. This statement refers only to male patients.

I have not sought to burden this paper with tabular analysis of this material, because I hope at a future date to present my experience in a form similar to that recently published by Colonel Harrison under the auspices of the Medical Research Council, Special Report Series, No. 132. At the moment I merely state the general conclusion arrived at; and it is this: that the principle of treatment embodied in these schemes constitutes the surest prophylactic against Wassermann-fastness and serological relapse. This is exactly the same conclusion as that arrived at by Moore and Kemp at the Johns Hopkins Hospital, where the same alternating method is adopted, but where mercury is used instead of bismuth. That my results are better and are obtained in a shorter period is due probably to just that fact, that I use the more potent bismuth.

The final testing of any line of treatment must be done by the histologist; and I feel a certain amount of justification for my belief—in view of the clinical and serological results—that when the tissues of patients treated according to the schemes I adopt are so investigated there will be found among them a very much lower proportion of uncured cases than in the Warthin series, or than will be found in cases treated upon the concurrent method.

Whether or not the duration of treatment in these schemes is sufficient to cause complete cure or sterilisa-

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tion cannot be decided until a histological investigation is carried out; but this much can be said, that under them there has not yet occurred a case of Wassermann-fastness.

In this we have, I think, a clue as to the cause—or at least the *principal* cause—of that condition.

It is generally accepted that the remedial agents themselves—arsenobenzene and bismuth—have little or no direct lethal action upon the *Treponema pallidum*, but that the sterilising effect is produced by a substance manufactured by the patient's tissues in response to the injection of these agents. The lethal substances themselves, which are probably of the nature of toxalbumins, may be conveniently respectively labelled "arsenoxyl" and "bismoxyl."

We provide the stimulus, and the patient's tissues work out his therapeutic salvation. The art of treatment consists in providing therapeutic stimuli in such a manner as to secure the most satisfactory response from the tissues. There is, in anti-syphilitic therapy, action and reaction taking place. And, just as in mechanics, the ideal is to secure an equilibrium. But in therapy there are complicating factors—biological factors—which do not enter into pure dynamics. The ideal here is to secure maximal reaction with minimal stimulus. We are dealing with living tissue reacting to non-vital stimuli. That tissue must not be damaged.

If, then, these chemical stimuli are applied too strongly, too often, or over too long a period, the reacting tissue may become exhausted—just as, in physiological work, muscle becomes exhausted to chemical or electrical stimulation. I am therefore in agreement with those who hold that the administration of arsenobenzene alone is essentially wrong. I agree that the patient must be treated with bismuth as well; but I do *not* agree that the two agents should be given at the same time.

The use of arsenobenzene alone, in too great amount or over too long a time, has a tendency to exhaust the reacting tissues. They become overworked—go on strike—and refuse to produce the arsenoxyl. A similar thing occurs if bismuth is used alone in the same manner. In addition, by too prolonged a use of one agent, even if the tissues continued to produce the necessary toxalbumin, the treponemata may develop a resistance to that

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substance. The end result will be the continued existence of living syphilitic organisms—that is, a condition of uncured syphilis such as Warthin sees, which may or may not exhibit itself by a persistent positive serology. In such cases, treatment along the same lines is obviously futile.

By the properly spaced-out alternating method, no chance is given to the tissues to become exhausted, and no chance to the treponemata to develop an immunity to the toxalbumin.

On the other hand, where the two agents—arsenobenzene and bismuth—are given concurrently, there is set up a terrific bombardment of the reacting tissues. They are asked to work overtime from the commencement; and they are deliberately encouraged to become exhausted and to “down tools.” Furthermore, by the concurrent method the treponemata are encouraged to develop a resistance to both toxalbumins at the same time.

Another point which may be mentioned incidentally here is that by concurrent administration the load thrown upon the liver and kidneys is very great indeed. Under the alternating scheme, jaundice, for example, is a thing of extreme rarity. And so likewise is nephritis. And, as I mentioned upon the last occasion when I spoke in this room, the few cases of jaundice we do see in Salford appear to be due to bismuth rather than to arsenobenzene. And I would suggest that a great deal of the jaundice which occurs under concurrent treatment, and which is practically always labelled “arsenical,” may be really due to bismuth. It is certainly very much less common under the alternating scheme, and I imagine that the reason is that the liver is subjected to a very much less severe bombardment.

My submission, then, is, first of all, that the prevention of Wassermann-fastness lies in combined therapy with arsenobenzene and bismuth, but that these drugs must be given in alternating series; and secondly, that when a condition of Wassermann-fastness does fall to be dealt with, the indications are, primarily, to rest the patient's tissues for a time, and, when treatment is resumed, it should be upon the alternating method.

So strongly do I feel upon this matter of treatment so as to avoid Wassermann-fastness and uncuredness, that when a patient is transferred to my clinic and is

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going to remain in the area for twelve months or more, when such a patient has had a small amount of concurrent treatment elsewhere, we try to persuade him to submit to Course No. 5. Again, for example, if a man attends suffering from a secondary eruption subsequent to inadequate treatment for a primary sore contracted a few months previously, we do not consider him to be suffering from early, but from *late*, syphilis. He, again, is immediately started off on Course No. 5. This is because experience has shown that Course No. 3 is insufficient in many instances to cure such patients. Their inadequate treatment means that they are heading for, or have already reached, Wassermann-fastness. They are, however, not considered to be definitely Wassermann-fast until they show a positive serology on the completion of Course No. 5.

We consider that early syphilis cannot possibly be Wassermann-fast, and we have never experienced a case which has become so under our *régime*. We consider that Wassermann-fastness indicates *late* syphilis, although every case of late syphilis is not necessarily, on that account, Wassermann-fast.

The criterion, then, that we have adopted for Wassermann-fastness may be stated thus :

That the patient has undergone fifty-four weeks of treatment according to Course No. 5, during which time he has received from 13 to 14 gm. of an arsenobenzene compound intravenously, and from 8 to 9 gm. of bismuth metal intramuscularly, in alternating series, and also that the fibrous tissue fortifications protecting the treponemata have been dissolved by giving large doses of iodides.

The frequency of Wassermann-fastness has been variously estimated ; and every estimate must differ from another according to two separate factors.

In the first place, the incidence of the condition depends in a great degree upon what standard is adopted for treatment. For example, there still exists a school which apparently hopes to cure primary syphilis with from six to eight injections of an arsenobenzene compound and a similar number of bismuth or mercury. We see many such. The case was perhaps originally sero-negative, and at the end of such a course it is naturally still sero-negative. The school I refer to appear to be content with that, and do not institute any further

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treatment until such time as the serology, being observed at intervals of from three to six months, again becomes positive. A good many of the cases we handle are of this kind, who suffer a serological relapse or who are Wassermann-fast. In the practice of those who treat syphilis along these lines—the chase after a negative Wassermann—the frequency of Wassermann-relapse and fastness must be very considerable—perhaps 20 per cent. In my view the inadequacy of the treatment is the direct stimulus which gives rise to the condition.

The higher the standard of treatment, the lower the incidence of Wassermann-fastness; and I submit that treatment is not adequate in which the aim is anything less than to reduce the incidence of Wassermann-fastness to zero. Even then we shall have to aim a little higher and strive to obtain a histological cure in 100 per cent. of cases of early syphilis.

Another important factor influencing the estimate as to the incidence of Wassermann-fastness is the sensitiveness of the test employed. An observer may think that he has a low incidence of Wassermann-fast cases and of relapses, whereas all that he has is a laboratory whose methods are not sufficiently delicate to uncover these conditions. And in this connection one would direct attention to the fact that a patient may be blood-negative, but at the same time the cerebro-spinal fluid may show pathological changes indicative of syphilis. Hence it is that, since comparatively few spinal fluid examinations are done, there may be in existence a great many cases of Wassermann-fastness—or uncured syphilis—so far as the central nervous system is concerned, which escape clinical and blood-serum recognition.

Being exclusively engaged in clinic work, I do not insist on lumbar or cisternal puncture as a routine, for exactly the same reason referred to by Colonel Harrison—namely, the fear of increasing defaulting. Were this done as a routine, however, then there would be found in any blood-negative series a proportion of cases which would fall into the category of neuro-recurrences; and, if very stringent criteria were adopted—for example, that of Becker at the Mayo Clinic, who considers an increase of cell count above ten to be a relapse—the incidence of recurrence would be very high, although the majority, or all, might escape clinical recognition.

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The pathological condition present in Wassermann-fastness appears to be one in which the infecting organisms have been driven into sites inaccessible to the action of the remedial agents ; that the tissues of the patient have more or less ceased to respond to therapeutic stimuli ; and that the organisms themselves have developed a degree of resistance to the drugs employed.

A careful clinical and X-ray examination will, in the vast majority of Wassermann-fast cases, reveal a visceral lesion. Post-mortem, such lesions are invariably present, although during life they may not have appeared above the clinical horizon. When clinical signs *are* present, the post-mortem findings are always much more extensive and severe than would have been expected.

Stokes and Busman found that the system most frequently involved in Wassermann-fast cases was the cardiovascular. This agrees with the Warthin post-mortem findings, and it is indeed exactly what one would expect in view of the fact that syphilis is essentially, first, last, and all the time, a disease of the cardiovascular system.

More than one type of involvement is the rule ; for example, in patients showing clinical evidence of neurosyphilis, in 50 per cent. the cardiovascular system is also clinically found to be involved. Post-mortem, this is so in 100 per cent. The essential pathology, then, of the condition of Wassermann-fastness appears to be the persistence of living treponemata ; it may be of a decreased degree of virulence, situated in the cardiovascular system chiefly, and setting up in some portion thereof the typical histological picture of a mild perivascular infiltration of lymphocytes and plasma cells, which reaction is of a progressive character in the direction of fibrosis and permanent structural damage to the organ or tissue involved.

The structural damage may be irreparable ; for instance, the fibrosis of the aortic ring may remain, and so in consequence will a resultant aortic incompetence. But nevertheless, although in such cases the patient must remain permanently "damaged goods," that is no reason why the *syphilis* should be considered incurable, and no reason why we should not attempt to cure it.

Whether or not we can do so is a very debatable matter ; but I do submit that the least we must aim for

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is to render the serology permanently negative. It is true that the attainment of this may not really indicate cure ; nevertheless, it is a step in that direction.

Now let us consider the matter of treatment, not only of the Wassermann-fastness, but of the Wassermann-fast patient.

In handling such a case, the first thing, in my view, is carefully to investigate the previous history with respect to the treatment given. The drugs used, their dosage, the routes by which they were administered, have all got to be considered. For example, if the patient has been treated with, say, N.A.B. intravenously, and with metallic bismuth intramuscularly, then it is clear that when treatment is resumed it will be useless to continue along the same lines. Sulfarsenol, or Myo-Salvarsan intramuscularly, or Silver-Salvarsan intravenously with the intramuscular injection of a soluble or insoluble bismuth salt, will lead to better results. To the original agents resistance has been developed, and such resistance cannot be broken down by these same agents without exceeding the limit of toleration.

If, again, the patient has developed Wassermann fastness as the result of treatment with arsenobenzene and mercury, the indication is to discard both these agents altogether, and to use bismuth alone. At a meeting of this Society in April, 1924, I mentioned then that I had, during the previous eighteen months, treated twenty-three patients who were Wassermann-fast as the result of the prolonged concurrent administration of N.A.B. and intramuscular mercury. These cases were submitted to three months' rest from antispecific treatment, but during that time they took large doses of potassium iodide—90 gr. a day. They were then treated with one of the early bismuth preparations—iodo-bismuthate of quinine, I think—and twelve became serologically negative. Having given up that particular clinic, I regret that I have no further information about these cases ; but the immediate response to a completely new line of attack was very striking and instructive.

The first principle, then, to be adopted in treating Wassermann fastness is to change the mode of attack. And an absolutely essential preliminary to that is to rest the tissues. That is equivalent to giving time for reinforcements to come up and to be trained. I consider this

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to be of paramount importance ; and perhaps I may be forgiven if I again seek to emphasise the point that it is the patient's tissues that cure his syphilis—we only supply the stimulus. The exhausted tissues must be got fit to resume the battle. They must be rested from previous over-stimulation. Three months' rest is not time lost ; it is essentially a saving both of time and of material.

During this rest period there is opportunity afforded for a careful examination of the patient in order to discover the location of the main damage. The course of future treatment largely depends upon this investigation. Indeed, the result of this examination may be such as to contra-indicate any further anti-specific treatment.

The discovery of a serious cardiovascular lesion must, in any case, give one pause. It may well be that in an elderly man the fibrosis which exists in his aorta may be the only rampart between him and death. The breaking-down of this by iodides may actually precipitate his decease. Such lesions may contra-indicate intravenous medication with arsenobenzene compounds ; and so, if these compounds are to be given, they must be of the type of sulfarsenol, and the route must be intramuscular or subcutaneous. The discovery of the principal site of the disease may call for the exhibition of bismuth alone. The age and circumstances of the patient may be such that treatment is not required—that the patient will not live long enough to enable cure or reduction in the strength of the serological reaction to take place.

Again, having identified the main trouble, some idea of the success of treatment may be gained from the clinical changes observed apart altogether from the serology.

And here I would like to venture the opinion that it is very desirable in dealing with Wassermann-fast cases for treatment to be controlled by serological tests which will show fairly fine gradations of the strength of the reaction.

Of course, the principal point in syphilis is whether or not the serum gives a positive result—apart altogether from the strength of the reaction or anything else, provided it is accepted that positive results mean syphilis and serve as an indication for treatment. But there is something more, and it is this : that if it be accepted that the degree of complement fixation varies directly

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with the degree of treponemal activity, then it becomes a matter of high importance to measure the strength of the reaction. To a certain extent this is already done by the Ministry of Health symbols ; but my submission is that in treating Wassermann-fast cases it is important to obtain more detailed information regarding the strength of the reaction during treatment than is possible under the Ministry symbols.

Our own laboratory in Salford has adopted the Ministry of Health method No. 4, but I do not consider that the system of reporting by the Ministry symbols is so valuable in gauging the progress of a Wassermann-fast case as is, for example, the quantitative method adopted by the Manchester Public Health Laboratory—although it is a rival establishment.

The Manchester method is a quantitative one with graduated dilutions of the patient's serum. The exact amount of hæmolysis in each tube is observed by means of a comparator and is recorded. "Standard fixation" is taken to be complete inhibition of hæmolysis. The reporting varies from "negative" through "doubtful" with standard fixation in dilutions from 1 in 1 to 1 in 2 ; "weakly positive" with standard fixation occurring in dilutions of from 1 in 3 to 1 in 8 ; "positive" where standard fixation occurs in dilutions from 1 in 10 to 1 in 20 ; and "strongly positive" where standard fixation takes place with dilutions of from 1 in 25 to 1 in 45. 1 in 45 is the strongest recorded or the greatest dilution tested.

Where some such quantitative method is not in use, a patient who was originally double plus in the Ministry symbols may still show a double plus at the end of, say, Course No. 5 ; but if the testing has been done by the quantitative method to which I refer, the original double plus reaction which was equivalent to standard fixation in a dilution of 1 in 45 may have actually been reduced to 1 in 25. The point I am seeking to show is that the one method illustrates very clearly the progress made, while the other does not. And the recognition of progress gives confidence to the patient, hope to the physician, and encouragement to both. I am aware of the disadvantages of the Manchester method ; but the solution may be in the performance of a quantitative flocculation test instead of the Wassermann in such Wassermann-fast cases.

In every case of syphilis, from the sero-negative primary

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stage onwards, the exhibition of iodides is called for, except in those late and grave cases of cardiovascular involvement already referred to. Fibrosis, behind which the treponemata shelter, is characteristic of late syphilis. The routine administration of iodides in early syphilis is a tolerably sure method of preventing the disease progressing to the late stage.

And when potassium iodide is given, it is, I believe, practically useless to give it in doses of less than 90 gr. a day. We have found that this dosage is better tolerated than a lower one; and certainly the clinical results are superior.

An Italian worker, Vercellino, has reported favourably upon the intravenous injection of sodium iodide, 1 to 10 gm. in 15 to 100 gm. of distilled water, daily or every second day. In all, thirteen cases of late syphilis were treated—endosyphilis, tabes, choroiditis, and congenital syphilis. In nine the serology became negative; and in five which were Wassermann-fast a negative result was obtained. No case of iodism occurred in the series.

Iodides alone, of course, have no curative value—they are merely to be used as solvents of fibrous tissue, and to open up the way for the action of arsenicals and bismuth. They increase the permeability of the tissues.

I have already alluded to the necessity for varying the mode of attack, and especially in avoiding the method and the medicaments previously used in producing the Wassermann-fast condition. There is another point, and it is: that before further active treatment is commenced, an attempt should be made to eliminate from the body any storage depôts remaining from former therapy. The eliminatory mechanism must be got into as satisfactory a state as possible. And in this respect, that important organ the *skin* is too frequently overlooked. A well-functioning skin is a high protection against toxic symptoms consequent upon treatment.

My former colleague at Wigan—Dr. Prosser White—was accustomed to treat all syphilitics by frequent hot sulphur baths; and under this *régime*, not only were untoward effects exceedingly rare, but the effect upon the serology was exceedingly good. Recently Cady and Ewerhardt have done some work along these lines upon “febrile body temperatures as possible adjunct treatment in Wassermann-fast patients.” Their conclusions are

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that while their investigation has not revealed any consistent evidence that hot baths are useful in Wassermann-fast syphilis, nevertheless, the improvement in the patient's sense of well-being, and the apparent serological responses in a proportion of cases, encourage them to continue the work.

My own experience is that the Turkish bath has a distinct value in such cases. There would seem to be at least two factors at work—stimulation of the skin, and pyrotherapy.

Although pyrotherapy—chemical or malarial—has been used chiefly in the treatment of paresis, it does give good results in other stages of syphilis. And, indeed, this is only to be expected when we consider that the essential pathology of syphilis is the same in every stage of the disease. The mechanism involved is a little obscure ; but this much seems clear, that the injection of a foreign protein induces a febrile reaction with an increase of immunity which appears to be non-specific in character. Non-specific protein therapy has a practical bearing upon the treatment of Wassermann-fastness, and should invariably be carried out.

The time selected for this should be during the rest-period—this is, before the resumption of truly anti-specific treatment. The preparations which we use are Aolan—a sterile milk protein—and Dmelcos, which is a vaccine prepared from Ducrey's bacillus, and given intravenously.

Aolan is given intramuscularly, and it has the effect when administered to a Wassermann-fast patient, in the absence of any arsenical and bismuth treatment, to cause, as a rule, the serological reaction, if not to become quite negative, at least to reduce it considerably in strength. And this may be obtained without any general reaction, so that the preparation is extremely suitable for out-patient work. It is also given intradermically. One has observed occasionally that the effect of Aolan may be provocative ; in other words, that under it an uncured sero-negative case will show a positive result ; and also that in a sero-positive case Aolan sometimes causes a temporary increase in the strength of the reaction.

Such an occurrence I regard as a good prognostic omen. I have at present a patient with a persistently negative serology, and who has had since 1927 recurrent cutaneous

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and mucous membrane syphilitic lesions. She has had a good deal of treatment elsewhere, with arsenic, bismuth and mercury. Her persistently negative serology with concurrent florid syphilis I interpret to mean a defective natural protection—a defective immunity-producing mechanism. Her tissues do not react to antispecific stimulation; and as long as her serology is negative for so long will arsenic and bismuth be wasted upon her. It may sound somewhat paradoxical, but really, in spite of her negative blood, she is equivalent to being Wassermann-fast. In this case, I do not propose to institute any anti-syphilitic treatment until protein therapy has converted her tissues into normally-reacting structures.

Rosner recently reported a similar case, in which it was not until the negative serology had been changed into a positive by the injection of luotestin, that active treatment was of any avail. In this respect it is interesting to remember that Moore and Kemp showed that a prematurely negative Wassermann test, and also a negative in untreated secondary syphilis, indicated a lack of resistance on the part of the patient.

The intravenous injection of Dmelcos causes a rapid and severe constitutional storm—rigors, and a temperature of perhaps 104. The effect is excellent, but the patient must remain in bed.

In conclusion, I would like to summarise my views as follows:

(1) Wassermann-fast syphilis is most easily prevented by combined therapy with arsenic and bismuth administered in alternating series over a sufficient period.

(2) Under this system previously untreated cases of early syphilis will be serologically cured in a period varying from twenty-four to forty weeks, according to the stage of the disease.

(3) Wassermann-fastness implies the presence of living treponemata and structural visceral damage of a progressively fibrotic character.

(4) The condition springs from exhaustion of the patient's tissues and the development of resistance by the treponemata.

(5) Treatment begins with prevention—avoidance of tissue exhaustion and drug resistance.

(6) The actual handling of the established condition implies: (a) Rest and rejuvenation of the tissues;

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(b) Elimination of previous storage depots ; (c) Dissolution of treponemal fibrous-tissue defences ; (d) Stimulation of natural immunity processes by injection of non-specific protein, and by general tonic treatment ; and finally, when antispecific treatment is recommenced, agents should be adopted which have not previously been used, and they ought to be applied in alternating series.

APPENDIX

STANDARD COURSES* FOR THE TREATMENT OF SYPHILIS IN THE VENEREAL DISEASES TREATMENT CENTRE.

City of Salford.

COURSE No. I.

EARLY PRIMARY SYPHILIS.

Treponema pallidum present.

Blood-Wassermann negative.

Stabilarsan once weekly for 6 weeks

Bismuth twice	„	4	„
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Stabilarsan once	„	6	„
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Bismuth twice	„	4	„
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Stabilarsan once	„	4	„
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Total	24	„
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Blood-Wassermann test seven days after last injection.

If *positive*, treat as Endosyphilis and give Course No. V.

If *negative*, discontinue treatment and apply test for Cure.

Criteria of Cure.—Give iodides for two weeks preceding each Wassermann test. A negative blood-Wassermann should be obtained every three months for one year after the cessation of treatment. Two years after the cessation of treatment, the blood and cerebro-spinal fluid (C.S.F.) must be negative after provocation.

If at any time during the observation period for cure the blood becomes positive, treat as Endosyphilis and give Course No. V.

COURSE No. II.

LATE PRIMARY SYPHILIS.

Treponema pallidum present.

Blood-Wassermann positive.

Stabilarsan once weekly for 8 weeks

Bismuth twice	„	8	„
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Stabilarsan once	„	8	„
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Bismuth twice	„	8	„
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Total	32	„
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* Courses No. IV., V. and VI. have recently been lengthened slightly as above. Through an oversight the amendment was not attached to the Courses which were distributed at the reading of the paper.

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Blood and C.S.F. Wassermann tests seven days after last injection.
If blood-Wassermann is *positive*, treat as Endosyphilis and give Course No. V.

If C.S.F. is *positive*, treat as Neurosyphilis and give Course No. VII.
If both blood and C.S.F. are *negative*, discontinue treatment and apply tests for cure.

Criteria of Cure.—As in Course No. I.

COURSE No. III.

EARLY SECONDARY SYPHILIS.

Blood-Wassermann positive.

General Cutaneous eruption.

Stabilarsan once weekly for 8 weeks		
Bismuth twice	6	„
Stabilarsan once	8	„
Bismuth twice	6	„
Stabilarsan once	6	„
Bismuth twice	4	„
Total	<u>38</u>	„

A blood and C.S.F. Wassermann is done one week after the last injection. If the blood is *positive*, treat as Endosyphilis and give Course No. V. If it is *negative*, discontinue treatment.

If C.S.F. is *positive*, treat as Neurosyphilis and give Course No. VII.
If *negative*, discontinue treatment.

Criteria of Cure.—As before.

COURSE No. IV.

LATE SECONDARY SYPHILIS.

Blood-Wassermann positive.

Fading General cutaneous eruption.

C.S.F. Negative.

Stabilarsan once weekly for 8 weeks		
Bismuth twice	8	„
Iodides . . . for 1 week		
Stabilarsan once weekly for 8 weeks		
Bismuth twice	8	„
Iodides . . . for 1 week		
Stabilarsan once weekly for 8 weeks		
Bismuth twice	8	„
Total	<u>50</u>	„

A blood and C.S.F. Wassermann is done one week after the last injection. If the blood is *positive*, and the C.S.F. *negative*, repeat the above course. If, however, the C.S.F. is *positive*, treat as Neurosyphilis and give Course No. VII.

If the blood and C.S.F. are both *negative*, discontinue treatment.

Criteria of Cure.—As before.

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COURSE No. V.

ENDOSYPHILIS.

Uncured cases without symptoms except a positive blood-Wassermann. C.S.F. negative. (If C.S.F. is positive, treat as Neurosyphilis and give Course No. VIII.)

Stabilarsan once weekly for 8 weeks	(Iodides)
Bismuth twice	„	8	„
Iodides for 4	„		
Stabilarsan once weekly for 8	„		
Bismuth twice	„	8	„
Iodides for 4	„		
Stabilarsan once weekly for 8	„		
Bismuth twice	„	8	„
Total		<u>56</u>	„

A blood and C.S.F. Wassermann is done one week after the last injection. If both are *negative*, cease the treatment. If C.S.F. is *positive*, treat as Neurosyphilis and give Course No. VII. If blood is *positive*, repeat Course No. V.

Criteria of Cure.—As before.

COURSE No. VI.

TERTIARY AND QUATERNARY SYPHILIS.

Skin, bone and mucous membrane asymmetrical lesions ; vascular and visceral involvement.

Blood-Wassermann positive.

C.S.F. negative. (If C.S.F. is positive, treat as Neurosyphilis and give Course No. VII.)

Stabilarsan once weekly for 8 weeks	(Iodides)
Bismuth twice	„	8	„
Iodides for 4	„		
Stabilarsan once weekly for 8	„		
Bismuth twice	„	8	„
Iodides for 4	„		
Stabilarsan once weekly for 8	„		
Bismuth twice	„	8	„
Iodides for 2	„		
Stabilarsan once weekly for 6	„		
Total		<u>64</u>	„

A blood and C.S.F. Wassermann is done one week after the last injection. If both are *negative*, cease treatment. If C.S.F. is *positive*, treat as Neurosyphilis and give Course No. VII. If blood is *positive*, give Course No. V.

Criteria of Cure.—As before

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COURSE NO. VII.

NEUROSYPHILIS.

Tabes dorsalis ; General Paralysis.

Cerebro-spinal Syphilis.

C.S.F. positive.

Colloidal gold test positive.

Cell count increased.

Bismuth twice weekly for 8 weeks

Tryparsamide once " 6 "
(*Lumbar drainage after last injection.*)

Iodides . . . for 4 weeks

Repeat the above Course till the cerebro-spinal fluid becomes serologically and cytologically normal.

A patient with Neurosyphilis must continue with treatment at frequent intervals for the remainder of life, no matter how long the cerebro-spinal fluid has been *negative*.

In early stages of general paralysis of the insane, the patient should be treated with Malaria inoculations.

COURSE NO. VIII.

CONGENITAL SYPHILIS.

Under five years of age.

Bismuth inunctions daily for 1 month.

Sulfarsenol intramuscularly for 2 months

Bismostab	"	3	"
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Sulfarsenol	"	3	"
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Bismostab	"	2	"
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Iodides	"	1	"
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Total	<u>12</u>	"
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For each of the succeeding four years, give two courses of treatment, each extending over a period of four months.

Bismuth intramuscularly for 1 month

Sulfarsenol	"	1	"
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Bismuth	"	1	"
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Sulfarsenol	"	1	"
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Total	<u>4</u>	"
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If at the end of five years Wassermann is *negative*, treatment is discontinued. If *positive*, give Course No. V.

Over five years of age.—Give Course No. V.